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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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(54) Title: A METHOD FOR TREATMENT OF PSORIASIS, BY OMEPRAZOLE OR RELATED COMPOUNDS

(57) Abstract

A method for treatment of psoriasis, characterized in administration of a therapeutically effective dose of omeprazole or related compounds.

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A method for treatment of psoriasis, by omeprazole or related compounds.

Field of invention

The present invention relates to a novel method of treating psoriasis.

Background of the invention

Psoriasis is a primary disease of the skin characterised by well-demarcated, inflammatory papules and plaques, which are typically covered by thickened scales. It is a disease of increased proliferation of epidermal cells, the precise cause of which is unknown.

The incidence of psoriasis in e.g. the US is about 2%. About 3% of whites and 1% of blacks are affected.

Therapeutic efforts in psoriasis are aimed at decreasing the proliferative rate of the epidermis either by direct action on cell division, or through agents that reduce the inflammatory response or vascular permeability. For patients with localised, limited psoriasis, topical administration of calcipotriol(D-vitamin derivative), dithranol or corticosteroids are the most convenient outpatient therapy. For patients with more extensive disease topical treatment followed by eradication with UV light may be necessary.

For patients with extensive disease a systemic antimitotic agent, such as methotrexate, can be used.

Extensive psoriasis can also be treated with photochemotherapy. In this regimen, orally administered, 8-methoxypsoralen produces photosensitization, which is followed by exposure to ultraviolet A (PUVA, 320 nm).

The retinoids, particularly eretrinate, either alone or in combination with PUVA, are also effective treatment for psoriasis. Furthermore, during acute attacks of pustular psoriasis, systemic steroids have been the therapy of choice.

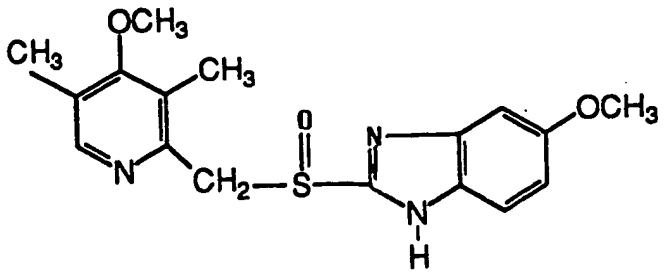
In view of postulated immunologic mechanisms it is interesting that cyclosporin A has been shown to be an effective treatment. Considering the risk for complications, such treatment should, however, be reserved for patients with recalcitrant, debilitating psoriasis when the benefit outweighs the potential risk of complications.

As will be clear from the above, there is a need for new, alternative and improved methods for treating psoriasis. The present invention provides a novel method for the treatment of psoriasis.

Detailed description of the invention

It has been found according to the invention that administration of omeprazole to patients affected by psoriasis results in disappearance of or great improvement of the symptoms of psoriasis. This applies to all manifestations of psoriasis.

Omeprazole is a pharmaceutical agent having the formula



and is used in therapy for treatment of gastric acid related diseases, such as gastric

ulcer.

Omeprazole can be administered orally, rectally or parenterally in neutral form or in the form of a basic salt, such as the Mg^{2+}, Ca^{2+}, Na^{+}, or K^{+} salts, preferably the Mg^{2+} or Na^{+} salts. While the effect on the symptoms of psoriasis have been established in patients who have taken omeprazole by the oral route, it is believed that the effect of omeprazole on psoriasis is a systemic effect which is not dependent on what mode of administration that is used, and that accordingly the healing effect on psoriasis will be seen also with other routes of administration such as rectal or parenteral administration.

Omeprazole can also be used in the form of a substantially pure enantiomer, or a salt thereof such as the salts mentioned above.

The commercially available pharmaceutical formulations of omeprazole will normally be used also for the use of omeprazole for treating psoriasis. Examples of such commercially available formulations are:

- pellets of omeprazole, packaged in capsules
- tablet containing omeprazole as active ingredient
- solutions for parenteral administration, comprising e.g. the sodium salt of omeprazole as active ingredient.

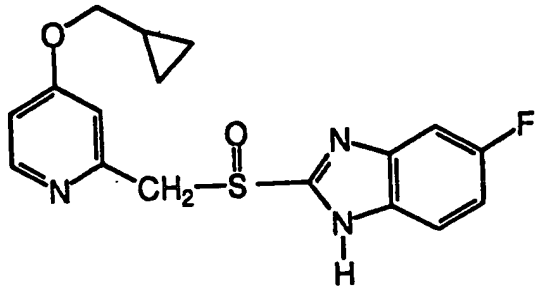
Being a labile compound with poor storage stability at neutral or acid pH, omeprazole formulations must be produced with great care. Examples of ways of producing stable formulations are given in e.g. EP-A-247,983.

The dose of omeprazole to be administered at treatment of psoriasis will vary

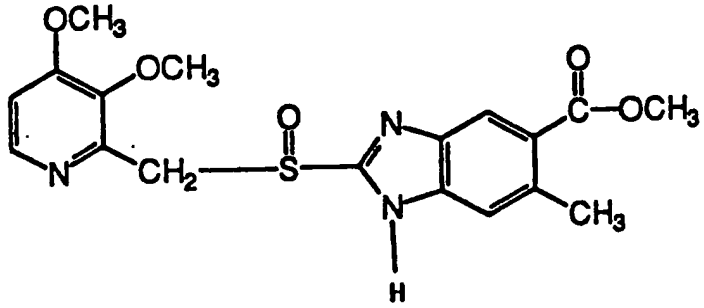
depending on factors such as the severity of the disease and the status of the patient. The dosage range at oral, rectal as well as i.v. administration may be in the interval from 1 to 100 mg per day. Normally, an amount of from 10 to 40 mg of omeprazole a day is envisaged at oral administration. A particularly suitable dosage may be in the range of 10-20 mg omeprazole per day.

Other compounds which can be used in the treatment of psoriasis in the same manner as omeprazole are the following:

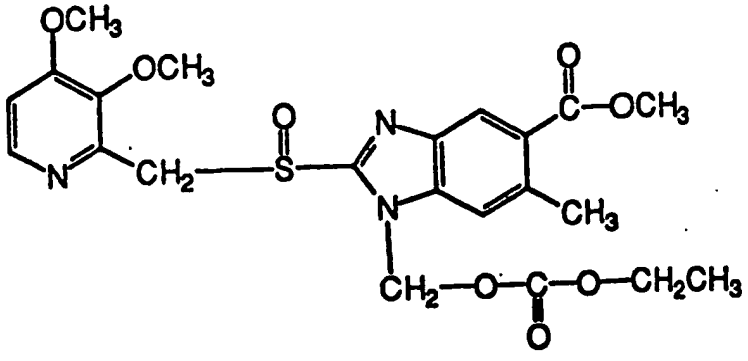
H 259/31



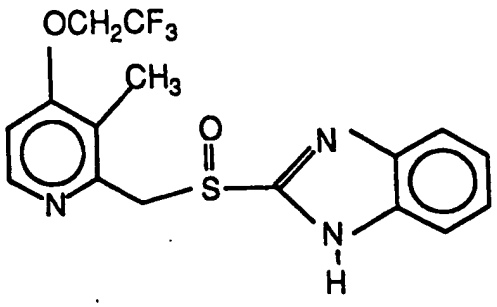
H 287/23



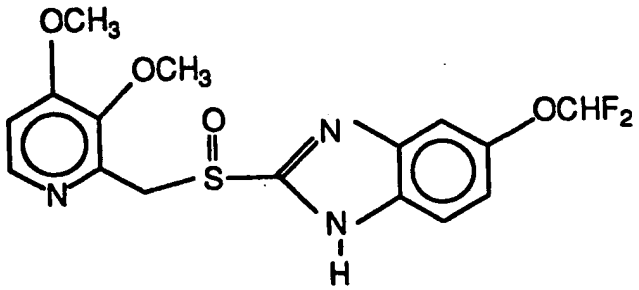
H 326/07



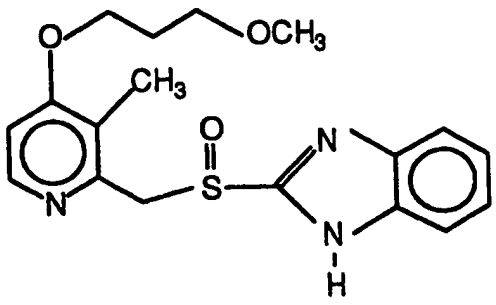
Lansoprazole



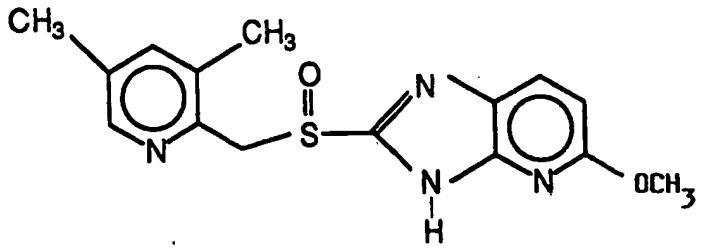
Pantoprazole



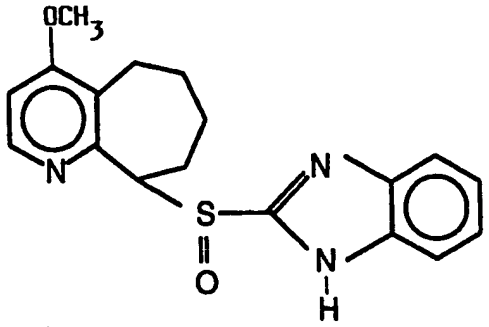
E-3810



TU-199



TY- 11345



Where applicable, a compound listed above may be used in racemic form or in the form of a substantially pure enantiomer. The compounds listed may be used in the same manner as described above for omeprazole, i.e. be administrated orally, rectally as well as parenterally. Parenteral administration is feasible provided that the compound is water soluble. Suitable compounds for parenteral administration are H 259/31, H 287/23, lansoprazole, pantoprazole, E-3810, TU-199 and TY-11345. Dosages to be administered can be in the same ranges as given above for omeprazole.

The invention is further exemplified by the following case studies. During oral treatment with omeprazole for acid related diseases, evidence has accumulated that omeprazole may be beneficial for treatment of psoriasis. Some examples are presented below:

Case 1 - 70-year-old woman

A 70 year old woman suffered since 53 years from typical chronic psoriasis vulgaris with main areas at both wrists as well as on her back. Treatment was, on basis of advice from her doctor, carried out with different gluco corticosteroids containing ointments as well as with salicyl-vaselin. However, the chronic state not changed.

Because of reflux esophagitis, degree III, the patient was treated since two years with omeprazole, once daily, 40 mg, evenings. After 3 weeks the patient noted for the first time the start of an improvement of her psoriasis. After 2 months, a clear improvement of the skin areas was established, an improvement which 2 years afterwards still was present. Already since the beginning of the improvement the patient used no external medicaments any longer.

Case 2 - 70-year-old man

Simultaneous disease: porphyria cutanea tarda. Widespread psoriasis in his whole life, partly controlled with topical treatment and PUVA treatment.

Because of acid-related disease treatment with ranitidin was initiated and due to lack of efficacy the treatment was, after a few months, changed to omeprazole. During one month's treatment with omeprazole the psoriatic condition improved considerably, but flared up again when the treatment was changed back to ranitidin. The condition improved again when omeprazole was re-instituted and the patient is currently under treatment with omeprazole for his psoriasis.

Case 3 - A 70-year-old man

with omeprazole since many years. Also father and sister have had psoriasis. The condition has been treated topically, but has never been completely controlled, especially not in the hair bottom.

When treatment with omeprazole was started because of a bleeding ulcer the psoriatic lesions healed completely, including the changes in the hair bottom, which was noted spontaneously by the barber. The psoriatic lesions returned when the omeprazole treatment was stopped.

Case 4 - A 60-year-old lady

with long-standing history of psoriasis. Whilst on omeprazole over a 3 month period there was a total and complete eradication of her psoriasis not only of the skin but of the finger nails. When omeprazole was stopped the condition started to recur.

Case 5 - A lady, age not known

who has been treated for severe psoriasis for some years. She has needed systemic treatment at times but has never really been clear of skin lesions. When treatment with omeprazole was started because of a gastric ulceration, her psoriasis started to clear up over a 5-week period.

Claims

1. A method for treatment of psoriasis, characterized in administration of a therapeutically effective dose of omeprazole.

2. A method according to claim 1, wherein omeprazole is administered orally.

3. A method according to claim 1, wherein omeprazole is administered parenterally.

4. A method according to claim 1, wherein omeprazole is administered rectally.

5. A method according to claims 1-4, wherein omeprazole in neutral form is administered.

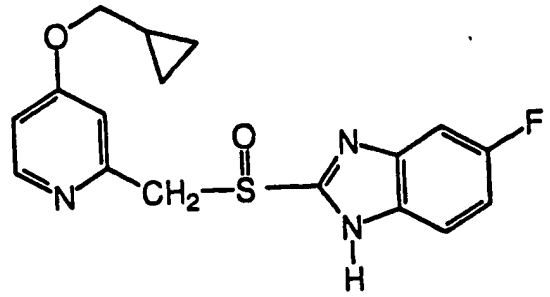
6. A method according to claims 1-4, wherein omeprazole is administered in the form of a basic salt, such as the magnesium salt or the sodium salt.

7. A method according to any of claims 1, 2, 3, 4, 5 or 6, wherein omeprazole is administered in a dose of from 1 to 100 mg per day.

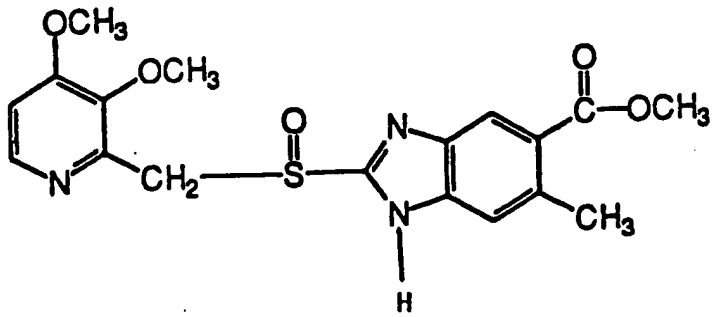
8. A method according to claim 7 wherein omeprazole is administered in a dose of from 10 to 40 mg per day.

9. A method for treatment of psoriasis, characterized in administration of a therapeutically effective dose of a compound selected from the group consisting of

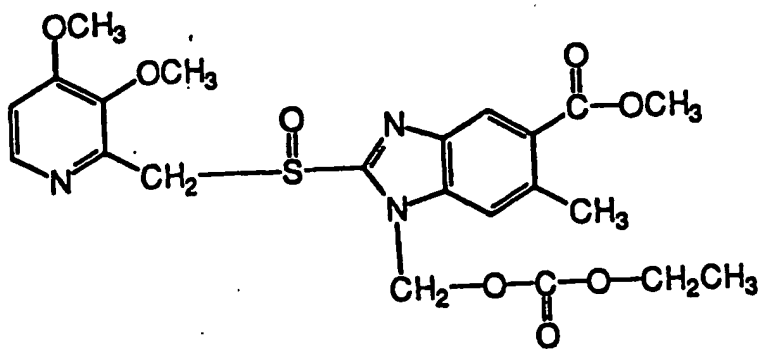
H 259/31



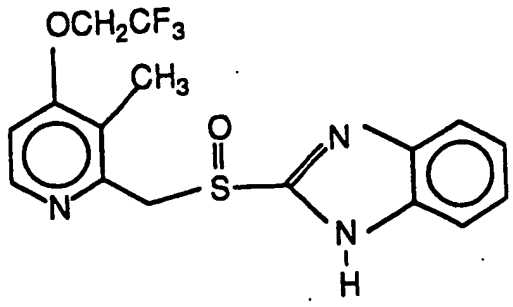
H 287/23



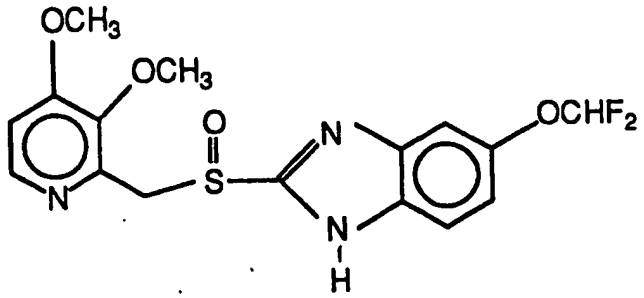
H 326/07



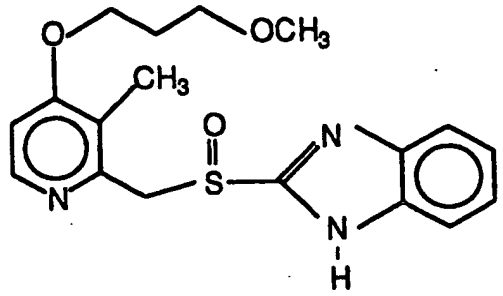
Lansoprazole



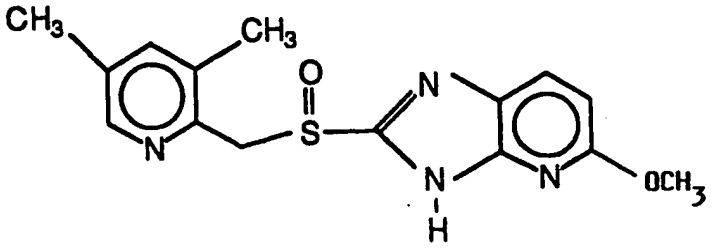
Pantoprazole



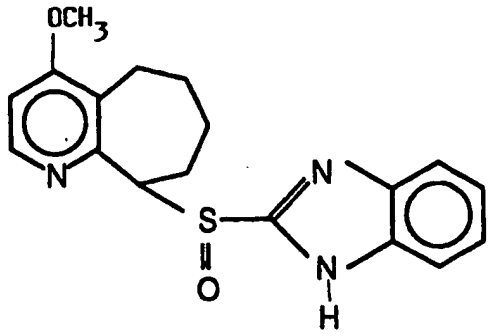
E-3810



TU-199



TY- 11345



10. A method according to claim 9, wherein the active substance is administered orally.

11. A method according to claim 9, wherein the active substance, such as H 259/31, H 287/23, lansoprazole, pantoprazole, E-3810, TU-199 or TY-11345, is administered parenterally.

12. A method according to claim 9, wherein the active substance is administered rectally.

13. A method according to claims 9-12, wherein the active substance in neutral form is administered.

14. A method according to claims 9-12, wherein the active substance such as H 259/31, H 287/23, lansoprazole, pantoprazole, E-3810, TU-199 or TY-11345, is administered in the form of a basic salt, such as the magnesium salt or the sodium salt.

15. A method according to any of claims 9, 10, 11, 12, 13 and 14, wherein the active substance is administered in a dose of from 1 to 100 mg per day.

16. A method according to claim 15 wherein the active substance is administered in a dose of from 10 to 40 mg per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00006

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/44, C07D 401/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Deutsche medizinische Wochenschrift, Volume 118, No 1-2, January 1993, W. Hasselkus, "Abheilung einer chronischen Psoriasis vulgaris unter Omeprazol" page 46 -- --------	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"E" erlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combinatic being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1994	10 -08- 1994
Name and mailing address f the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized fficer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00006

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
see the attached sheet

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

The claims relate to a method for treatment of the human or animal body by therapy which this International Searching Authority is not required to search under the provisions of Article 17(2)(a)(i) of PCT and Rule 39.1(iv) of the Regulations under PCT. Nevertheless, a search has been executed, which is based on the alleged effects of omeprazole.